Express Mail No.: EV 654 850 792 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Dall'Acqua *et al.*	Confirmation No.:	2678
Serial No.:	10/020,354	Art Unit:	1644
Filed:	December 12, 2001	Examiner:	BELYAVSKYI, M.A.
For:	MOLECULES WITH EXTENDED HALF-LIVES, COMPOSITIONS AND USES THEREOF	Attorney Docket No:	10271-027 CAM #209073-999026

DECLARATION OF DR. WILLIAM F. DALL'ACQUA UNDER 37 C.F.R. §1.132

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, WILLIAM F. DALL'ACQUA, do declare that:

1. I presently hold the position of Associate Director, Department of Protein Engineering, at MedImmune, Inc., a corporation organized under the law of the State of Delaware and located at One MedImmune Way, Gaithersburg, MD 20878 (herein referred to as "MedImmune"). Other positions I have held are set forth in my *curriculum vitae*, attached hereto as **Exhibit 1**.

2. I am a co-inventor of the invention disclosed and claimed in the above-identified patent application. I previously reviewed the application, including the claims, and executed a declaration in connection with the application on May 17, 2002.

3. My education, technical experience and professional activities, honors and awards, and list of recent publications are set forth in my *curriculum vitae*, attached hereto as Exhibit 1. I have worked extensively in the area of immunology and, in particular, the area of antibody structure and function.

4. I understand that the pending claims are directed to antibody compositions having particular amino acid substitutions in the heavy chain constant region of a gamma globulin

molecule, which substitutions are indicated in the claims by amino acid positions numbered according to the EU index as set forth in the three volume reference book Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, 5th ed., 1991 NIH Pub. No. 91-3242 (hereinafter "the Kabat reference"). I have been informed that the claims of the above-identified patent application are rejected by the Examiner as indefinite and also as lacking enablement. In particular, I understand that the recitation of amino acid positions "numbered according to the EU index as in Kabat" in the claims is considered indefinite by the Examiner. The Examiner's concern arises from the belief that, because different laboratories may use different numbering systems for the IgG constant domain, a reference sequence is needed in the claims to indicate the amino acid positions at which the claimed substitutions are to be made. I further understand that the Examiner's enablement rejection is based on the Examiner's view that the tables of the Kabat reference must be provided in the specification because they are necessary to practice the claimed invention, *i.e.*, to determine which amino acids are to be substituted according to the claims.

5. The Kabat reference was a well known reference text that was widely used by those of skill in the art of antibody structure at the time of the earliest claimed priority of this application, i.e., as of December 12, 2000. The Kabat reference continues to be regarded by those of skill in the art as a useful and important reference text.

6. Unlike many proteins, the heavy chain constant region ("CH") of immunoglobulin molecules is typically numbered according a standardized numbering scheme. This standardization is possible because the CH region is highly conserved in terms of overall structure. Specifically, the CH region of an immunoglobulin molecule is divided into three structural "domains" referred to as the CH1, CH2, and CH3 domains. These domains share a high degree of sequence homology. In fact, among antibodies of the same isotype, the CH region is practically invariant (see *e.g.*, page 47, col. 1, of Abbas et al. 1991 *Cellular and Molecular Immunology*, attached hereto as **Exhibit 2**)(stating that the heavy chain constant region "is invariant among the member antibodies within a particular isotype"). The "IgG" recited in the claims of the subject application refers to an antibody molecule of the "gamma" globulin isotype. It is this sequence similarity in the CH region of IgG molecules that allowed

for the development of a common numbering scheme applicable to all IgG CH regions. This numbering is referred to as "EU numbering" or "the EU index."

7. The EU index is a standard numbering scheme for numbering the CH region of IgG molecules. It is based on the numbering of the first complete sequence of an IgG molecule, the "Eu" protein, published by Edelman in 1969. (see Edelman *et al.* 1969 *Proc. Natl. Acad. Sci. U.S.A.* 63:878-85, attached as **Exhibit 3**). Since the Eu protein was the first IgG molecule to be completely sequenced, the numbering of the Eu protein was adopted as the reference standard against which subsequently sequenced IgG molecules were compared. The sequence of the Eu protein is one of a number of IgG sequences provided in the Kabat reference (see col. 28 at page 680 and reference no. 28 at page 719 of the Kabat reference in Exhibits 7 and 8, respectively).

8. As early as 1991, the EU index was such an art-recognized standard for numbering immunoglobulin CH regions that it was included by Kabat alongside the "Kabat numbering" scheme in his seminal reference text, *Sequences of Proteins of Immunological Interest* (see *e.g.*, the Kabat tables of CH2 and CH3 regions provided in Exhibits 7 and 8). The Kabat reference provides, *inter alia*, about 60 aligned sequences of immunoglobulin CH1, CH2 and CH3 regions (see *e.g.*, the CH2 table beginning on page 679 (**Exhibit 4**) and the CH3 table beginning at page 688 (**Exhibit 5**)). Each of these sequences is identified in the list of notes beginning at page 719 (**Exhibit 6**).

9. By the time of the earliest claimed priority of the subject application, December 12, 2000, the EU index was well-established as a standard numbering scheme for the CH region of IgG molecules. In fact, the convention of EU numbering was so commonplace that it was often used in the literature without citing to the Kabat reference. See *e.g.*, Brekke *et al.* 1993 *Nature* 363:628-630 (abstract)("EU numbering"); Tao *et al.* 1993 *J. Exp. Med.* 178:661-667 (Table 1 at page 662)("residue number is based on the EU system"); and Idusogie *et al.* 2000 *J. Immunol.* 164:4178-4184 (Fig. 3 page 4181)("the EU nomenclature is used"), attached hereto as **Exhibits 7-9**, respectively.

10. The inclusion of the EU index in the Kabat reference has ensured its continued recognition as a standard numbering scheme for immunoglobulin CH regions. Moreover,

because the Kabat tables show the EU index alongside Kabat numbering, the Kabat reference also provides a table for conversion between the two numbering systems.

11. The number of sequenced immunoglobulin molecules has increased substantially since the Kabat reference was published in 1991. These sequences are now generally published as searchable databases accessible through the internet rather than as printed volumes of tables. However, the numbering of these molecules remains standardized according to the scheme set forth in the Kabat reference.

12. Given an amino acid residue numbered according to the EU index as in Kabat, it is a matter of routine skill to determine the corresponding amino acid position in other immunoglobulin molecules using the Kabat tables. For example, given a CH sequence of an IgG molecule, one first finds the best alignment of that CH sequence with one of the CH reference sequences provided in the Kabat tables. This can be done using routine methods. Once a good alignment is made, it is simply a matter of reading the table to identify an amino acid at a particular position according to the EU index. For example, given a residue number of 252, one first finds the tables of aligned CH sequences in the Kabat references then reads down the EU index column of numbers to position "252." (See page 679 of the Kabat reference in Exhibit 6). Tracing across this row identifies the amino acid at position 252 for each of the aligned sequences. Thus, one can see that residue no. 252 is a glycine ("Gly") in the human IgM sequences (*e.g.*, at col. 1 and 2), a methionine ("Met") in the human IgG sequences (*e.g.*, at col. 14, 28, 47, 48, and 53) and a leucine ("Leu") in the human IgA sequences (*e.g.*, col. 41 and 42).

13. In view of the high degree of amino acid sequence identity in the CH region of immunoglobulins of the same isotype, it is a matter of routine skill to align any given CH region sequence with the immunoglobulin CH sequences of the Kabat reference and thereby determine the identity of an amino acid residue at a particular EU numbered position. In practice, such alignments are routinely carried out using computer programs that are readily available in the art. However, the sequence similarity in the CH region of molecules of the IgG isotype is so high that it is also possible for one of skill to make a reasonably good alignment by hand.

14. The "EU index" as published in the Kabat reference thus provides a standard numbering scheme applicable to the CH region of any IgG molecule. The Kabat reference also provides

numerous CH region reference sequences aligned and numbered according to the EU index (see e.g., pages 679-696, and references cited therein, listed on pages 719-723). This standard numbering scheme allows researchers to refer to the position of an amino acid residue in any IgG CH region by referencing its position according to the EU index, without the need to publish the entire sequence of the particular IgG molecule at issue.

15. A statement that an amino acid position in the CH region of an IgG molecule is "residue number "*x*" according to the EU index as in Kabat" has a definite and precise meaning to one of skill in the art. Moreover, the EU index is so well-established that a reference to "EU numbering" will continue to have a clear and definite meaning to those of skill in the art for the foreseeable future.

16. The amino acid substitutions intended by the claims of the above-identified patent application, which are identified by their position number according to the EU index as set forth in the Kabat reference, are clear and definite without the need to provide a reference sequence.

17. I declare further that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified patent application or any patent issuing thereon.

Dated: 10/03/05

WILLIAM F. DALL'ACQUA, Ph.D.

Attachments:

Exhibit 1: *Curriculum Vitae* of William F. Dall'Aqua
Exhibit 2: Abbas et al. 1991 *Cellular and Molecular Immunology*
Exhibit 3: Edelman *et al.* 1969 *Proc. Natl. Acad. Sci. U.S.A.* 63:878-85
Exhibit 4: Kabat *et al.* 1991 *Sequences of Proteins of Immunological Interest*, 5th ed., NIH Pub. No. 91-3242 (pages 679-687)
Exhibit 5: *Id.* pages 688-696
Exhibit 6: *Id.* pages 719-723
Exhibit 7: Brekke *et al.* 1993 *Nature* 363:628-630
Exhibit 8: Tao *et al.* 1993 *J. Exp. Med.* 178:661-667
Exhibit 9: Idusogie *et al.* 2000 *J. Immunol.* 164:4178-4184